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Electrophysiological abnormalities in subjects with lone atrial fibrillation – Too little, too late?

1. Electrophysiological parameters as surrogates for atrial remodeling

Arroja and colleagues present an interesting observational study providing insights into the electrophysiological characteristics of subjects with atrial fibrillation (AF) and no evidence of overt structural heart disease in this issue of the journal [1]. The authors utilized signal-averaged P-wave duration and intracardiac electrophysiological parameters (intra and inter-atrial conduction times and refractory periods) to qualify the presence of subclinical atrial structural damage (atrial remodeling) in subjects with AF. They compared the prevalence of electrophysiological parameters of atrial remodeling in subjects with AF undergoing catheter ablation to that in a control cohort of subjects without AF. The study also compared parameters of subclinical atrial remodeling in subjects with and without recurrence of AF after catheter ablation. The rationale, presumably was to test the hypothesis that subclinical atrial remodeling in subjects undergoing catheter ablation for AF may be associated with a higher incidence of AF recurrence.

As expected the surrogate parameters of subclinical atrial remodeling (P-wave duration and intracardiac electrophysiological measurements) were abnormal in subjects with AF compared to subjects without AF. This finding is not novel or unique to the current study and the fact that subjects with AF and no evidence of overt structural heart disease can have subclinical atrial remodeling has been demonstrated previously by multiple investigators [2–7]. In the current study, no differences were noted in the prevalence of surrogate parameters of atrial remodeling in subjects with and without AF recurrence after catheter ablation. Even though the study is methodologically sound and well executed, it was not designed to detect a clinically meaningful difference in surrogate parameters of subclinical atrial remodeling between subjects with and without AF recurrence. The reason for this is that the study included a homogenous group of subjects with paroxysmal AF, who in general tend to have less atrial remodeling as shown in previous mechanistic studies evaluating the prevalence of electrophysiological markers of atrial remodeling (in paroxysmal and persistent AF phenotypes) [8]. The low prevalence of electrophysiological parameters and minimal severity of atrial remodeling in subjects included in the study predicated that a relatively large sample size had to be enrolled to demonstrate a clinically meaningful difference. The number of subjects included in the study was unfortunately inadequate to answer this question.

Secondly, in the current study subjects underwent pulmonary vein isolation (PVI) by the wide area circumferential ablation (WACA) technique using either the 'point-by-point' ablation technique or a variable, circular-multipolar catheter. A previous mechanistic study had shown that PVI performed by the WACA technique was likely to cause greater atrial remodeling, as demonstrated by surrogate electrophysiological parameters (signal averaged P-wave duration), compared to a segmental approach. The better success rates associated with the WACA technique was attributed to a greater degree of modification of the atrial substrate (positive remodeling) compared to the segmental PVI technique [9]. The fact that all subjects in the current study underwent PVI using the WACA technique should have resulted in nearly similar extent of atrial substrate modification after catheter ablation and should not have influenced the incidence of AF recurrence. This explanation is also supported by the observation that pulmonary vein reconnection (PVR) was the exclusive mechanism responsible for AF recurrence observed in subjects undergoing repeat catheter ablation in the current study.

2. Redefining the concept of "lone" atrial fibrillation

The authors also analyzed a subgroup of subjects with so called "lone" AF, defined as subjects below 60 years of age and without systemic hypertension. Individuals with "lone" AF were observed to have the same prevalence and severity of electrophysiological parameters of subclinical atrial remodeling like that noted in subjects with systemic hypertension or older than 60 years of age. The authors imply that electrophysiological parameters of atrial remodeling may be useful in identifying subjects at risk of developing AF without obvious risk factors or evidence of overt structural heart disease. However, this inference may be not entirely accurate.

The term "lone" AF was introduced almost seven decades ago by Evans and Swann to describe a subset of subjects with AF and no apparent risk factors known to be associated with AF [10]. This archaic term was used to describe subjects with AF in whom investigations (available at the time) did not reveal structural heart disease related to known etiologies such as ischemic heart disease, valvular heart disease etc., and implied that the AF was "idiopathic".

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However, a recent white paper on this subject has provided a series of cogent arguments dissuading the use of this terminology, primarily because a plethora of sophisticated techniques available for imaging the ultrastructural details of atrial myocardium, detecting biomarkers linked to atrial inflammation and somatic genetic abnormalities in the atrial myocardium have dramatically broadened our understanding of the pathogenesis of AF [11–17]. Therefore, it is not surprising that subjects with so called "lone" AF in the current study were also found to have electrophysiological features suggestive of atrial remodeling. This highlights the fact that all subjects with AF have abnormalities of the atrial myocardium that may be either clinically evident (overt structural heart disease) or may be detected using sophisticated techniques to evaluate the ultrastructural and genetic composition of atrial myocardium. In other words, electrophysiological testing may be a rather unsophisticated and insensitive tool to identify subjects at risk for developing AF or those with a propensity to respond sub-optimally to catheter ablation. It is increasingly apparent that all subjects with AF (in the absence of reversible causes) have abnormal atrial myocardium and that at present we simply do not have the sensitive techniques required to identify all of these abnormalities.

3. Developing strategies for detecting atrial remodeling in subjects without overt structural heart disease

The reported prevalence of AF in subjects without any overt evidence of structural heart disease is between 0.2% and 68% depending on the definition of "lone" AF, the population being evaluated and diagnostic modalities used to detect abnormalities of atrial myocardium [18–21]. The extent to which novel imaging techniques, biomarkers and genetic tests, beyond the obvious assessment of cardiac structure and function using echocardiography, should be used to detect abnormalities of atrial myocardium and predict the future risk of developing AF has not been clearly specified or widely accepted [11,22–25]. Developing an optimal strategy for diagnostic evaluation of subjects at risk of or with manifest AF is one of the most difficult challenges facing the clinician.

4. Precision medicine for the management of atrial fibrillation

The ultimate objective of the clinician is to be able to tailor therapy precisely to target the unique genetic and ultrastructural abnormalities in an individual subject with AF. The hope is that identification of atrial myocardial abnormalities very early on in the course of the disease, much before the manifestation of electrophysiological parameters of atrial remodeling or overt structural abnormalities are apparent, may offer an opportunity to better prognosticate outcomes, initiate measures for primordial prevention of AF and develop precision therapies [26–28]. In conclusion, even though the current article does not describe a novel, unique or more sensitive technique to identify subjects with atrial remodeling or prognosticate outcomes in subjects undergoing catheter ablation, it definitely highlights the need for ongoing research to develop tools and strategies for early detection and targeted therapy of AF.

Disclosures

None of the authors have any disclosures or conflicts of interest for this subject.

References

[1] Arroja JD, Burri H, Park CI, Giraudet P, Zimmermann M. Electrophysiological abnormalities in patients with paroxysmal atrial fibrillation in the absence of overt structural heart disease. Indian Pacing Electrophysiol J 2016;16(5):152–6.

[2] Morillo CA, Klein GJ, Jones DL, Guiraudon CM. Chronic rapid atrial pacing. Structural, functional, and electrophysiological characteristics of a new model of sustained atrial fibrillation. Circulation 1995;91(5):1588–95.

[3] Capucci A, Biffi M, Boriani G, Ravelli F, Nollo G, Sabbatani P, et al. Dynamic electrophysiological behavior of human atria during paroxysmal atrial fibrillation. Circulation 1995;92(5):1193–202.

[4] Kumagai K, Akimitsu S, Kawahira K, Kawanami F, Yamanouchi Y, Hiroki T, et al. Electrophysiological properties in chronic lone atrial fibrillation. Circulation 1991;84(4):1662–8.

[5] Fukunami M, Yamada T, Ohmori M, Kumagai K, Umemoto K, Sakai A, et al. Detection of patients at risk for paroxysmal atrial fibrillation during sinus rhythm by P wave-triggered signal-averaged electrocardiogram. Circulation 1991;83(1):162–9.

[6] Simpson Jr RJ, Foster JR, Mulrow JP, Gettes LS. The electrophysiological substrate of atrial fibrillation. Pacing Clin Electrophysiol PACE 1983;6(5 Pt 2):1166–70.

[7] Attuel P, Childers R, Cauchemez B, Poveda J, Mugica J, Coumel P. Failure in the rate adaptation of the atrial refractory period: its relationship to vulnerability. Int J Cardiol 1982;2(2):179–97.

[8] Blanche C, Tran N, Rigamonti F, Burri H, Zimmermann M. Value of P-wave signal averaging to predict atrial fibrillation recurrences after pulmonary vein isolation. Europace Eur Pacing Arrhythm Cardiac Electrophysiol J Work Groups Cardiac Pacing Arrhythm Cardiac Cell Electrophysiol Eur Soc Cardiol 2013;15(2):198–204.

[9] Redfearn DP, Skanes AC, Gula LJ, Griffith MJ, Marshall HJ, Stafford PJ, et al. Noninvasive assessment of atrial substrate change after wide area circumferential ablation: a comparison with segmental pulmonary vein isolation. Ann noninvasive Electrocardiol Of J Int Soc Holter Noninvasive Electrocardiol Inc 2007;12(4):329–37.

[10] Evans W, Swann P. Lone auricular fibrillation. Br heart J 1954;16(2):189–94.

[11] Wyse DG, Van Gelder IC, Ellinor PT, Go AS, Kalman JM, Narayan SM, et al. Lone atrial fibrillation: does it exist? J Am Coll Cardiol 2014;63(17):1715–23.

[12] Ueberham L, Bollmann A, Shoemaker MB, Arya A, Adams V, Hindricks G, et al. Genetic ACE I/D polymorphism and recurrence of atrial fibrillation after catheter ablation. Circulation Arrhythm Electrophysiol 2013;6(4):732–7.

[13] Everett BM, Cook NR, Conen D, Chasman DI, Ridker PM, Albert CM. Novel genetic markers improve measures of atrial fibrillation risk prediction. Eur Heart J 2013;34(29):2243–51.

[14] Tiffany Win T, Ambale Venkatesh B, Volpe GJ, Mewton N, Rizzi P, Sharma RK, et al. Associations of electrocardiographic P-wave characteristics with left atrial function, and diffuse left ventricular fibrosis defined by cardiac magnetic resonance: the PRIMERI Study. Heart Rhythm Of J Heart Rhythm Soc 2015;12(1):155–62.

[15] Canpolat U, Oto A, Hazirolan T, Sunman H, Yorgun H, Sahiner L, et al. A prospective DE-MRI study evaluating the role of TGF-beta1 in left atrial fibrosis and implications for outcomes of cryoballoon-based catheter ablation: new insights into primary fibrotic atriocardiomyopathy. J Cardiovasc Electrophysiol 2015;26(3):251–9.

[16] Hijazi Z, Siegbahn A, Andersson U, Granger CB, Alexander JH, Atar D, et al. High-sensitivity troponin I for risk assessment in patients with atrial fibrillation: insights from the Apixaban for Reduction in Stroke and other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. Circulation 2014;129(6):625–34.

[17] Hijazi Z, Oldgren J, Siegbahn A, Granger CB, Wallentin L. Biomarkers in atrial fibrillation: a clinical review. Eur Heart J 2013;34(20):1475–80.

[18] Jahangir A, Lee V, Friedman PA, Trusty JM, Hodge DO, Kopecky SL, et al. Long-term progression and outcomes with aging in patients with lone atrial fibrillation: a 30-year follow-up study. Circulation 2007;115(24):3050–6.

[19] Kopecky SL, Gersh BJ, McGoon MD, Chu CP, Ilstrup DM, Chesebro JH, et al. Lone atrial fibrillation in elderly persons: a marker for cardiovascular risk. Arch Intern Med 1999;159(10):1118–22.

[20] Kopecky SL, Gersh BJ, McGoon MD, Whisnant JP, Holmes Jr DR, Ilstrup DM, et al. The natural history of lone atrial fibrillation. A population-based study over three decades. N. Engl J Med 1987;317(11):669–74.

[21] Nieuwlaat R, Capucci A, Camm AJ, Olsson SB, Andresen D, Davies DW, et al. Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. Eur Heart J 2005;26(22):2422–34.

[22] European Heart Rhythm A, European Association for Cardio-Thoracic S, Camm AJ, Kirchhof P, Lip GY, Schotten U, et al. Guidelines for the management of atrial fibrillation: the task force for the management of atrial fibrillation of the European society of cardiology (ESC). Eur Heart J 2010;31(19):2369–429.

[23] Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, et al., 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: a report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Developed in

partnership with the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology (ESC) and the European Cardiac Arrhythmia Society (ECAS); and in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), and the Society of Thoracic Surgeons (STS). Endorsed by the governing bodies of the American College of Cardiology Foundation, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, the Asia Pacific Heart Rhythm Society, and the Heart Rhythm Society. Heart Rhythm: J Heart Rhythm Soc 2012;9(4). 632–696 e21.

[24] Verma A, Cairns JA, Mitchell LB, Macle L, Stiell IG, Gladstone D, et al. 2014 focused update of the canadian cardiovascular society guidelines for the management of atrial fibrillation. Can J Cardiol 2014;30(10):1114–30.

[25] January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland Jr JC, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation 2014;130(23):2071–104.

[26] Van Gelder IC, Hobbelt AH, Marcos EG, Schotten U, Cappato R, Lewalter T, et al. Tailored treatment strategies: a new approach for modern management of atrial fibrillation. J Intern Med 2016;279(5):457–66.

[27] Lip GY, Potpara T, Boriani G, Blomstrom-Lundqvist C. A tailored treatment strategy: a modern approach for stroke prevention in patients with atrial fibrillation. J Intern Med 2016;279(5):467–76.

[28] Fabritz L, Guasch E, Antoniades C, Bardinet I, Benninger G, Betts TR, et al. Expert consensus document: defining the major health modifiers causing atrial fibrillation: a roadmap to underpin personalized prevention and treatment. Nat Rev Cardiol 2016;13(4):230–7.

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